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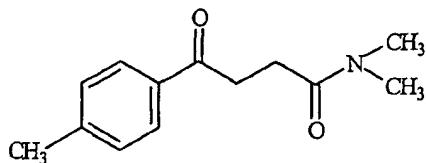
(54) Title: SYNTHESIS OF N,N-DIMETHYL-3-(4-METHYL) BENZOYL PROPIONAMIDE, A KEY INTERMEDIATE OF ZOLPIDEM

(57) Abstract: The present invention relates to an improved and industrially advantageous process for the preparation of N,N-dimethyl-3-(4-methyl)benzoyl propionamide, which compound is a key intermediate for the synthesis of zolpidem hemitartrate, a non-benzodiazepine hypnotic agent.

**SYNTHESIS OF N, N-DIMETHYL-3-(4-METHYL) BENZOYL
PROPIONAMIDE, A KEY INTERMEDIATE OF ZOLPIDEM**

FIELD OF THE INVENTION

The present invention relates to an improved and industrially advanced process for the preparation of N, N-dimethyl-3-(4-methyl)benzoyl propionamide of Formula I



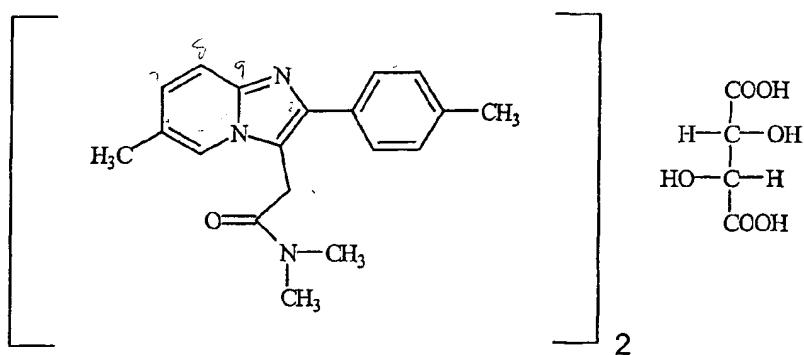
FORMULA I

which compound is a key intermediate for the synthesis of zolpidem hemitartrate, a non-benzodiazepine hypnotic agent.

BACKGROUND OF THE INVENTION

Chemically, zolpidem hemitartrate is N, N,6-trimethyl-2-(4-methyl-phenyl)-imidazo[1,2-a]pyridine-3-acetamide L-(+)-hemitartrate of Formula II

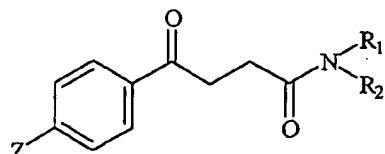
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FORMULA II

Zolpidem is known from European Patent No. 50,563 (U.S. Patent No. 4,382,938 is its equivalent in the United States) assigned to Synthelabo. The pharmacological profile of this compound is characterized by a strong hypnotic effect, together with weak anticonvulsant and muscle-relaxant properties, showing selectivity for benzodiazepine receptors with the biochemical characteristics and regional distribution of the benzodiazepine one subtype. While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex and shares some of the pharmacological properties of the benzodiazepines. The selective binding of zolpidem on the omega-1 receptor may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies. Zolpidem shows both high affinity and selectivity toward non-benzodiazepine-2 receptors which means improved activity and/or fewer side effects for the treatment of anxiety, sleep disorders and convulsions.

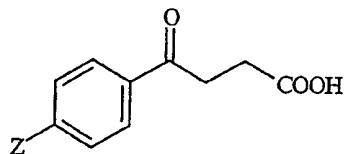
A previously known general method for the synthesis of the intermediate N, N-dialkyl-3-benzoyl-propionamide of Formula III



FORMULA III

wherein for zolpidem intermediate $Z=CH_3$ and $R_1 = R_2 = CH_3$ was reported in *J. Med. Chem.*, 40, 3109 - 3118 (1997) which involves reaction of 3-benzoyl propionic acid of Formula IV

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FORMULA IV

[$Z=CH_3$, prepared by the method as described in *J. Org. Chem.*, 24, 1759-1763 (1959)] with the required dialkylamines (dimethylamine for Zolpidem) in the presence of ethyl 1,2-dihydro-2-ethoxy-1-quinoline carboxylate (EEDQ) in tetrahydrofuran at reflux. Evaporation of the solvent under reduced pressure and pH adjustment gives the crude product which in turn is purified by column chromatography.

The above method described in the prior art for the manufacture of the desired compound of Formula I suffers from the following limitations:

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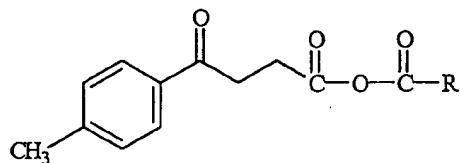
- The reaction conditions are unsafe which are burdened with the risk of explosion and fire as the reaction makes use of the solvent tetrahydrofuran at reflux temperature.
- The process requires commercially limited available and costly raw material such as ethyl 1,2-dihydro-2-ethoxy-1-quinoline carboxylate (EEDQ).

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The process involves column chromatography for purification of the desired intermediate which is not practically feasible at the commercial scale.

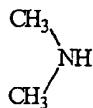
It is an object of the present invention to solve the problems associated with the prior art, to provide an improved and efficient method for the preparation of pure N, N-dimethyl-3-(4-methyl) benzoyl propionamide of Formula I. The process provides obvious benefits with respect to economics, convenience to operate at a commercial scale and does not require chromatography to purify the desired product.

More particularly, the present invention relates to a process for the preparation of N, N-dimethyl-3-(4-methyl)benzoyl propionamide of Formula I, comprising reacting 3-(4-methyl)-benzoyl propionic acid of Formula IV (wherein Z is methyl) with alkyl chloroformate or pivaloyl chloride to give mixed anhydride of Formula V



FORMULA V

wherein R is alkyl or substituted alkyl, preferably methyl, ethyl or tertiary butyl, in a suitable solvent in the presence of an organic base, the mixed anhydride of Formula V on further reaction with dimethylamine of Formula VI



FORMULA VI

affords the desired product of Formula I.

5 The alkyl chloroformate is selected from the group consisting of methyl chloroformate, ethyl chloroformate and butyl chloroformate methyl chloroformate being preferred. The alkyl chloroformate or pivaloyl chloride is suitably used in an amount of 1.0 - 2.0 molar equivalents of compound of Formula IV, and preferably in an amount of 1.1 to 1.5 molar equivalents.

10 The term "suitable solvent" includes chlorinated solvents, aromatic solvents, esters and mixture(s) thereof. Preferably, the solvent may be selected from the group consisting of dichloromethane, dichloroethane, chloroform, toluene, ethyl acetate and mixture(s) thereof. The solvent is suitably used in an amount of 5 to 20 times of weight of the compound of
15 Formula IV, and preferably in an amount 10 to 15 times.

20 The suitable organic base is selected from the group comprising trimethylamine, triethylamine, picolines, pyridine, pyridine derivatives, morpholine and morpholine derivatives. The organic base is suitably used in an amount of 1.0 to 2.0 molar equivalents of the compound of Formula IV and
preferably in an amount 1.1 to 1.5 molar equivalents.

The reaction of "mixed anhydride" of Formula V (wherein R is the same as defined earlier) with dimethylamine is carried out at a selected temperature

range of -25 to 40°C, preferably 0 to 30°C during a period of 15 minutes to several hours, preferably for about 15 minutes to 1 hour. The desired compound, N, N-dimethyl-3-(4-methyl) benzoyl propronamide of Formula I is isolated by removal of the solvent completely from the organic layer after 5 washing with water/aqueous sodium carbonate solution and stirring the residue with n-hexane. The solid separated is filtered, washed with n-hexane and dried to get the pure desired compound.

In the following section preferred embodiments are described by way of examples to illustrate the process of this invention. However, these are not 10 intended in any way to limit the scope of the present invention.

PREPARATION OF N, N-DIMETHYL-3-(4-METHYL)BENZOYL PROPIONAMIDE

EXAMPLE 1

3-(4-Methyl)-benzoyl propionic acid (50gm) was suspended in ethyl acetate (500ml) and it was cooled to 0-5°C. To it was added triethylamine (28.93gm) at 0-5°C to get a clear solution. Pivaloyl chloride (34.52gm) was added to the clear solution during a period of 15 minutes keeping temperature at 0-5°C. The resulting reaction mixture was stirred at 0-5°C for about 30 minutes. To this was added dimethyl amine(60gm, 40% solution in water) in 20 one lot taken in 250ml of ethyl acetate at -10 to 0°C. After stirring it at 0 to 10°C for about 30 minutes, the reaction mixture was washed with water, aqueous sodium carbonate solution (10% w/v) and water. The organic layer was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure. The residue so obtained was stirred with hexane and the

solid separated was filtered and dried to get 48.5 gm (yield 85% of the theory) of pure title compound (purity by HPLC 99.8%).

EXAMPLE 2

Triethylamine (28.93 gm) was added to a solution of 3-(4-methyl)-5 benzoyl propionic acid (50gm) dissolved in methylene chloride (500ml) at about -5°C. The resulting reaction mixture was further cooled to about -10°C and pivaloyl chloride (34.52gm) was added to it during a period of about 15 minutes keeping the temperature at -10 to 0°C. The resulting reaction mixture was stirred at -2 to 0°C for about 30 minutes and dimethyl amine (60gm, 40% 10 w/v solution in water) was added to it in one lot. The reaction mixture thus obtained was further stirred at 25-30°C for about 30 minutes, washed with water, aqueous sodium carbonate solution (10% w/v) and finally with water. The organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum. Hexane (200ml) was added to the residue, the 15 solid separated was filtered and dried to get 46.8 gm (82%) of the pure product (Purity by HPLC 99.7%).

EXAMPLE 3

Triethylamine (14.5gm) was added to solution of 3-(4-methyl)-benzoyl propionic acid (25gm) in chloroform (250ml) at 0-5°C. The solution thus 20 obtained was cooled to -5°C and pivaloyl chloride (17.3gm) was added to it over a period of about 20 minutes keeping the temperature at -5 to 0°C. The reaction mixture thus obtained was stirred at -5 to 0°C for about 30 minutes and to it was added dimethylamine (30gm, 40% w/v solution in water) at -5 to 0°C during a period of about 15 minutes. The reaction mixture thus obtained

was further stirred at -5 to 0°C for about 15 minutes, washed with water, 10% w/v aqueous sodium carbonate solution and finally with water. The organic layer was concentrated, and the residue was stirred with hexane. The solid separated was filtered and dried to get 23.5gm (yield 82.5% of the theory) of 5 the pure desired product (purity by HPLC = 99.8%).

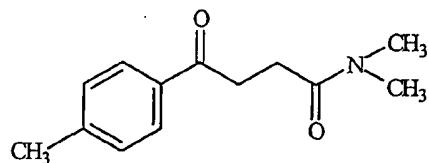
EXAMPLE 4

To a solution of 3-(4-methyl)-benzoylpropionic acid (25gm) in 10 methylene chloride (250ml) at 0°C was added triethylamine (14.5gm). The resulting reaction mixture was cooled to -25°C and ethylchloroformate (14.2gm) was added to it at -25 to -20°C during a period of about 10 minutes. The reaction mixture thus obtained was stirred at -25 to -20°C for about 30 15 minutes and dimethylamine (30gm, 40% w/v solution in water) was added at about -25°C during a period of about 10 minutes. The reaction mixture thus obtained was stirred at the -10 to 0°C for about 30 minutes and raised the temperature to about 25-30°C. The resulting reaction mixture was washed with water, aqueous sodium carbonate solution (10% w/v) and finally with water. The organic layer was concentrated under vacuum and stirred with hexane (100ml). The solid thus separated was filtered and dried to yield 23 20 gm (yield 80.7% of theory) of the desired product (purity by HPLC 99.8%).

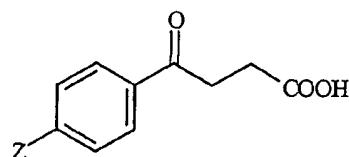
While the present invention has been described in terms of its specific 20 embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

CLAIMS:

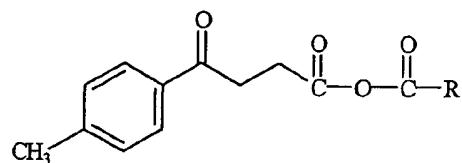
1. A process for the preparation of N, N-dimethyl-3-(4-methyl) benzoyl propionamide of Formula I

**FORMULA I**

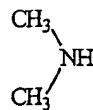
comprising reacting 3-(4-methyl)-benzoyl propionic acid of Formula IV

**FORMULA IV**

wherein Z is methyl, with alkyl chloroformate or pivaloyl chloride in a suitable solvent in the presence of an organic base to afford mixed anhydride of Formula V

**FORMULA V**

wherein R is alkyl or substituted alkyl and further reacting mixed anhydride of Formula V with dimethylamine of Formula VI



FORMULA VI

2. The process of claim 1 wherein the alkyl chloroformate is selected from the group consisting of methyl chloroformate, ethyl chloroformate and butyl chloroformate.
3. The process of claim 2 wherein the alkyl chloroformate is methyl chloroformate.
4. The process of claim 1 wherein suitable solvent consists of chlorinated solvents, aromatic solvents, esters and mixture(s) thereof.
5. The process of claim 4 wherein the solvent is selected from the group consisting of dichloromethane, dichloroethane, chloroform, toluene, ethyl acetate and mixture(s) thereof.
6. The process of claim 1 wherein organic base is selected from the group consisting of trimethylamine, triethylamine, picolines, pyridine pyridine, derivatives, morpholine, morpholine derivatives and mixtures thereof.
7. The process of claim 1 wherein alkylchloroformate is used in an amount of 1.0 to 2.0 molar equivalents of compound of Formula IV.
8. The process of claim 1, wherein solvent is used in amount of 5 to 20 times (by volume) of weight of the compound of Formula IV.

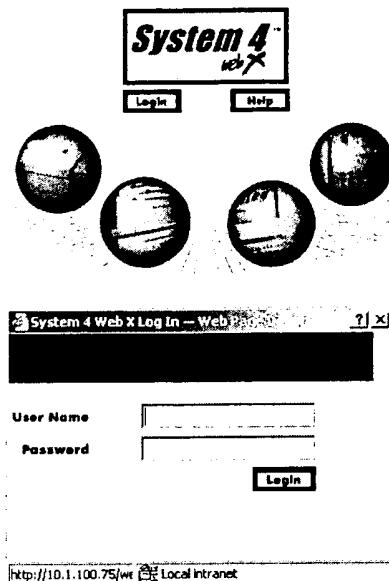
9. The process of claim 8, wherein solvent is used in an amount of 10 to 15 times (by volume) of weight of the compound of Formula IV.
10. The process of claim 1, wherein the organic base is used in an amount of 1.0 to 2.0 molar equivalents of compound of Formula IV.
11. The process of claim 10, wherein the organic base is used in an amount of 1.1 to 1.5 molar equivalents of compound of Formula IV.
12. The process according to claim 1, wherein the reaction of mixed anhydride of Formula V with dimethylamine is carried out at a selected temperature range of -25 to 40°C.
13. The process according to claim 12, wherein the reaction of mixed anhydride of Formula V with dimethylamine is carried out at a temperature of about 0 to 30°C.
14. The process according to claim 1, wherein the reaction of mixed anhydride of Formula V with dimethyl amine is carried out for 15 minutes to several hours.
15. The process according to claim 14, wherein the reaction of mixed anhydride of Formula V with dimethylamine is carried out for about 15 minutes to 1 hour.
16. The process of claim 1 further comprising suitable work up after the reaction is complete.

17. The process according to claim 16, wherein the work up comprises removal of the solvent from the organic layer and isolation of said product by stirring the remaining residue with hexane.

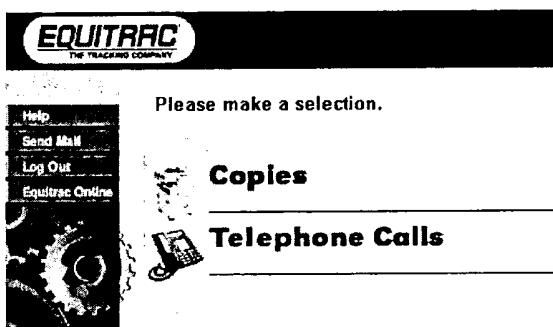
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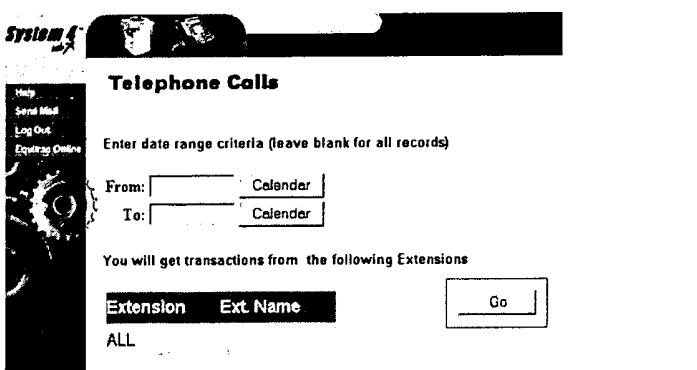
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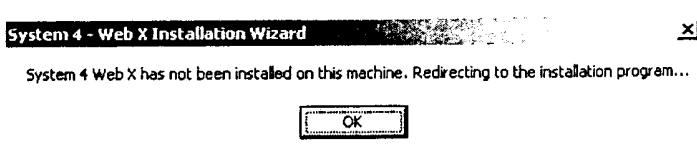
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